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08/758,033	11/27/96	CLAYMAN G	INGN:022

EXAMINER

HALIDA,K

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/758,033	Applicant(s) Clayman, G.
	Examiner Karen M. Hauda	Group Art Unit 1819

☒ Responsive to communication(s) filed on *Nov 24, 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-137* is/are pending in the application.

Of the above, claim(s) *21-25* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20 and 26-137* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant's application was filed November 27, 1996. Claims 1-137 are pending.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-20 in Paper No. 9, filed November 24, 1997 is acknowledged.

Claims 21-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 9.

Applicant is reminded to cancel the non-elected claims.

Claim Rejections - 35 USC § 112

Claims 1-20 and 26-137 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting tumor growth in some cancers comprising the administration of a vector construct encoding the wild-type p53 protein at or around the tumor site, wherein exogenously introduced p53 protein expression results in the inhibition of tumor growth , does not reasonably provide enablement for methods of **treating any and all cancers** comprising the administration of a vector construct encoding any p53 polypeptide by **any and all** administration modes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

1-20 and 26-137

JMC 2/16/98

It is initially noted that claims ~~1-37~~ are directed to methods of treating a subject having a tumor, wherein said tumor comprises cells which express functional p53 polypeptide. All other claims are directed to methods of treating a subject having a tumor, wherein said tumor may or may not have cells expressing functional p53 polypeptide. As indicated by applicants in their specification, the ability of tumor cells which express a functional p53 polypeptide to undergo apoptosis following the delivery of exogenous p53 polypeptide was a surprising result and is contrary to what was known about p53 as a tumor suppressor gene (see specification pages 7-8). Applicants assert that this phenomenon can be applied to numerous types of tumor cells, however, the specification and the art lack any evidence that tumor cells other than squamous cell carcinomas expressing functional p53 polypeptide can undergo apoptosis following the delivery of exogenous p53 polypeptide. It is unclear whether this is a phenomenon unique to squamous cell carcinomas or is indeed applicable to any and all cancers. Since the mechanisms of this "phenomenon" are unknown, and the specification and art are absent evidence that this unique response applies to other cancers the claims are limited to treatment of SCC which express functional p53 polypeptide. Furthermore, Liu et al. taught that there appear to be "inherent constitutive differences" between various cancers, suggesting that this phenomenon is not applicable to all cancers (see page 3122 first paragraph).

With respect to all claims, applicant's specification fails to enable **any and all** methods of delivering nucleic acid constructs, **any and all** nucleic acid constructs, and **any and all** combination treatments. Although the gene therapy art has made drastic improvements in the past

decade such that treatment of patients having cancer via the administration of vectors encoding specific proteins is being realized, the state of the gene therapy art was not so predictable at the time of applicants effective filing date, that the skilled artisan could readily combine gene therapy comprising p53 with any other gene thought to have potential in cancer therapy without undue experimentation. Many of applicants claims are directed to combination therapy comprising the administration of a vector encoding a p53 protein combined with the administration of a vector encoding another therapeutic gene. These alternative therapeutic genes encompass **any** other gene, but more specifically, numerous cytokine genes and/or numerous other genes thought to be involved in cancer progression. The specification fails to provide guidance to the skilled artisan on what levels these genes need to be expressed, which promoters/enhancers can provide sufficient expression of these genes, at what proportions the vectors are to be delivered, etc. Additionally, even if the skilled artisan could determine the mode and method of delivery, there is insufficient support within the specification that the combination of any or all of these alternative therapeutic genes would or could provide a therapeutic response. For example, cytokines are known in the art to alter the immune system by acting on specific or varying cells (depending on the cytokine). The mechanisms and modes of action of many cytokines are poorly understood, but it is well recognized that the increased expression of one cytokine can upregulate or downregulate the expression of other cytokines. Applicant's specification fails to provide any guidance to the skilled artisan on what combinations of cytokines or other genes would effectively stimulate the immune system to provide a treatment effect on tumors. Thus, the skilled artisan

would be required to undergo undue experimentation to determine the parameters and specific combination of the numerously claimed therapeutic genes with p53 gene treatment given the unpredictably immune response to combination therapy, the absence of guidance provided by the specification, the absence of teachings in the prior art, the unpredictable state of the gene therapy art, and the breadth of the claims.

Applicant's claims additionally read on **any and all** administration modes as long as the expression construct is delivered to the tumor. However, the specification fails to provide guidance to the skilled artisan on mechanisms which can delivery the vector construct to the tumor with a reasonable expectation of success. The unpredictability of gene therapy and vector targeting is supported by the teachings of Culver et al., Hodgson et al. and Miller et al. Culver et al., reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (page 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that "[d]eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pages 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to

be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Although applicants specification supports direct delivery of vectors by direct injection into the tumor site or by catheter delivery, the specification fails to provide guidance to the skilled artisan on methods which can efficiently target the gene construct to the tumor cells. Thus, the specification only enables direct delivery at or around the tumor site.

Applicants claims additionally read on the delivery of **any and all** expression constructs, however, the specification only provides support for delivery expression and construction for adenoviral vectors. Although numerous other expression constructs are known in the art, the predictability of *in vivo* expression of these expression constructs had not been demonstrated prior to applicant's effective filing date (see Culver et al., Hodgson et al., or Miller et al, for example). Therefore, even if the skilled artisan could construct the appropriate expression constructs, there is no guidance within the specification or the art for the parameters and specifics to utilize these vectors *in vivo*.

Applicant's claims read on the delivery of any portion of a p53 polypeptide which may be wild-type or mutant. However, the specification only enables the delivery of adenoviral vectors encoding functional wild-type p53 protein. There is no evidence that the delivery of mutant p53 polypeptide or portions of p53 polypeptide can induce apoptosis. Furthermore, if either mutant p53 polypeptide or portions of p53 polypeptide could induce apoptosis, the specification fails to provide guidance to the skilled artisan on which portions or mutants could achieve this function.

The evidence in the art and applicant's specification only supports the delivery and expression of wild-type p53 protein to induce apoptosis.

Finally, applicant's claims read on any "treatment" response to "subjects" having cancer. The specification only supports the inhibition or regression of tumor growth. There is no evidence within the specification that the claimed treatment can cure cancer. Additionally, the specification fails to support treatment for tumors in **any and all** subjects. The specification only describes isolation and construction of genes from mammalian species. The specification and the art is absent any evidence that p53 is involved in cancer onset or regression in species other than mammals.

Therefore, for the reasons presented above, the specification only enables the *in vivo* delivery of adenoviral vectors encoding wild-type p53 protein at or around the tumor site. Additionally, with the exception of squamous cell carcinoma, the specification only enables the delivery of wild-type p53 protein to tumor cells which are lacking functional p53 expression.

Claims 1, 15, 38, 74, and 109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 38, 74, and 109 are indefinite because the claim lacks a step which ties the steps of delivery an expression construct to the subject back to the preamble of treating the patient. It is unclear how "administration" results in "treatment". Additionally, the term "treatment in these

claims is indefinite because it is unclear what response is encompassed in treatment. is mere delivery of the expression construct enough to constitute treatment? Does treatment mean cure? A "wherein" clause defining the scope of treatment is suggested. Note: Claims 1, 38, 74 and 109 also do not require expression of the p53 gene product by the cell.

Claim 15 is indefinite because the term "expression vector" lacks antecedent basis. Additionally, claim 15 does not further limit claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1; 3, 11, 15, 16, 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. (Cancer Research, Vol. 55 (1995)) or Clayman et al. (Cancer Research, Vol. 55 (1995)).

Liu et al. taught the method of reducing tumor burden in a mouse following the administration of an adenoviral vector encoding a wild-type p53 polypeptide to a squamous cell carcinoma tumor *in vivo* wherein the squamous cell carcinoma expressed functional p53 polypeptide. Thus, the claimed invention was anticipated by Liu et al.

Clayman et al. taught the method of reducing tumor burden in a mouse following the administration of an adenoviral vector encoding a wild-type p53 polypeptide to a squamous cell carcinoma tumor *in vivo* wherein the squamous cell carcinoma expressed functional p53 polypeptide. Thus, the claimed invention was anticipated by Clayman et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20 and 26-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Cancer Research, Vol. 55 (1995)), Liu et al. (Cancer Research, Vol. 54 (1994)) or Clayman et al. (Cancer Research, Vol. 55 (1995)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) in view of Zhang et al. or Brahmwell.

Liu et al. (Cancer Research, Vol. 55 (1995)) taught the method of reducing tumor burden in a mouse following the administration of an adenoviral vector encoding a wild-type p53 polypeptide to a squamous cell carcinoma tumor *in vivo* wherein the squamous cell carcinoma expressed functional p53 polypeptide.

Clayman et al. (Cancer Research, Vol. 55 (1995)) taught the method of reducing tumor burden in a mouse following the administration of an adenoviral vector encoding a wild-type p53 polypeptide to a squamous cell carcinoma tumor *in vivo* wherein the squamous cell carcinoma expressed functional p53 polypeptide.

Liu et al. (Cancer Research, Vol. 54 (1994)) taught the growth suppression of squamous cell carcinoma of human head and neck cancer (SCCHN) established *in vivo* in nude mice following the administration of adenoviral vectors encoding wild-type p53. At page 3666, column 2, Liu et al. state that the regression in cancer burden in nude mice was at least 60 times more than in the experimental controls. Liu et al. did not teach that expression of wild-type p53 by SCCHN cancer cells made the cancer cells susceptible to radiation therapy.

Wills et al. (Human Gene Therapy, Vol. 5 (1994)) taught inhibition of tumor proliferation and tumorigenicity following a single injection of recombinant adenoviral vectors encoding wild-type p53 protein into carcinoma cell lines grown either *in vitro* or into established tumor *in vivo* in a nude mouse. Wills et al. additionally taught that repetitive administration of adenoviral vectors encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example). Additionally, at page 1086, column 2, Wills et al suggests that the ability to express wild-type p53 in cancer cells may increase the tumor cells susceptibility to radiation therapy or chemotherapy. Specifically, Wills et al. state:

> Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may have become so due in part to the lack of wild-type p53. **By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy.**

(emphasis added). Wills et al. does not teach administration and reduction of tumor burden for treatment of squamous cell carcinoma.

Each of Zhang et al. or Brahmwell taught the advantage to combination therapy. Specifically, Zhang et al. reviews various treatments for cancer and concludes at page 505 that with respect to cancer therapy, combinational approaches with using gene therapy, chemotherapy, immunotherapy, radiotherapy, and surgery is the most logical and has the greatest potential for a more advanced therapy. Brahmwell reviews various chemotherapies and discusses the benefits of combining such therapies.

Therefore, given the above teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify combine the methods of any one of Liu et al. (Cancer Research, Vol. 55 (1995)), Liu et al. (Cancer Research, Vol. 54 (1994)) or Clayman et al. (Proceedings of AACR, Vol. 36 (1995)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) with that of Zhang et al. or Brahmwell and treat cancer with adenoviral vectors encoding p53 polypeptide with a reasonable expectation of success. The ordinary artisan would have been motivated to combine these references because they all discuss therapeutic models for treating cancer.

Applicant is reminded that the claimed invention does not require expression of the exogenous p53 polypeptide by the cells, or define any specific treatment response.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda KMH
Patent Examiner
Febrary 15, 1998

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